

**PATENT COOPERATION TREATY**  
**PCT**  
**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**  
(Chapter II of the Patent Cooperation Treaty)  
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2003IT304	<b>FOR FURTHER ACTION</b>		See Form PCT/IPEA/416
International application No. PCT/IB2004/003448	International filing date (day/month/year) 21.10.2004	Priority date (day/month/year) 22.10.2003	
International Patent Classification (IPC) or national classification and IPC C07H19/06, C07H1/00			
Applicant CLARIANT LIFE SCIENCE MOLECULES (ITALIA) S.P.A.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 4 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> <i>(sent to the applicant and to the International Bureau) a total of 2 sheets, as follows:</i></p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> <i>(sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</i></p> <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion  <input type="checkbox"/> Box No. II Priority  <input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  <input type="checkbox"/> Box No. IV Lack of unity of invention  <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement  <input type="checkbox"/> Box No. VI Certain documents cited  <input type="checkbox"/> Box No. VII Certain defects in the international application  <input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 07.04.2005	Date of completion of this report 06.03.2006		
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer de Nooy, A Telephone No. +31 70 340-2338		



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International application No.  
PCT/IB2004/003448

**INTERNATIONAL PRELIMINARY REPORT  
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**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
  - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
    - international search (under Rules 12.3 and 23.1(b))
    - publication of the international application (under Rule 12.4)
    - international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

**Description, Pages**

1-7 as originally filed

**Claims, Numbers**

1-8 received on 21.11.2005 with letter of 16.11.2005

- a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
- 3.  The amendments have resulted in the cancellation of:
  - the description, pages
  - the claims, Nos.
  - the drawings, sheets/figs
  - the sequence listing (*specify*):
  - any table(s) related to sequence listing (*specify*):
- 4.  This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
  - the description, pages
  - the claims, Nos.
  - the drawings, sheets/figs
  - the sequence listing (*specify*):
  - any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/IB2004/003448

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N)	Yes: Claims	1-8
	No: Claims	
Inventive step (IS)	Yes: Claims	1-8
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-8
	No: Claims	

**2. Citations and explanations (Rule 70.7):**

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.

PCT/IB2004/003448

**Re Item V****Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following document:

D1: US4340729

The document D1 is regarded as being the closest prior art to the subject-matter of claims 1-8, and shows (column 3 lines 27-41, column 5 lines 34-60) the synthesis of a protected doxifluridine derivative using a Lewis acid where this catalyst is added at 0°C.

The subject-matter of claims 1-8 differs from this known subject matter in that the Lewis acid is added below -10°C.

The subject-matter of claims 1-10 is therefore new (Article 33(2) PCT).

The technical effect of this difference (see examples of the present application) is that a higher yield with less impurities is obtained.

The problem to be solved by the present invention may be regarded as the provision of an improved method for the synthesis of doxyfluridine.

The solution to this problem proposed in claims 1-8 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons: although it would be obvious for the skilled person, when trying to improve the synthesis of doxifluridine to vary the reaction conditions given in D1, it is unexpected that such a significant increase in yield and decrease of impurities is obtained as in the present case (see examples) by lowering the temperature. Since in D1 there is no incentive of lowering the temperature below 0°C, an inventive step is acknowledged.

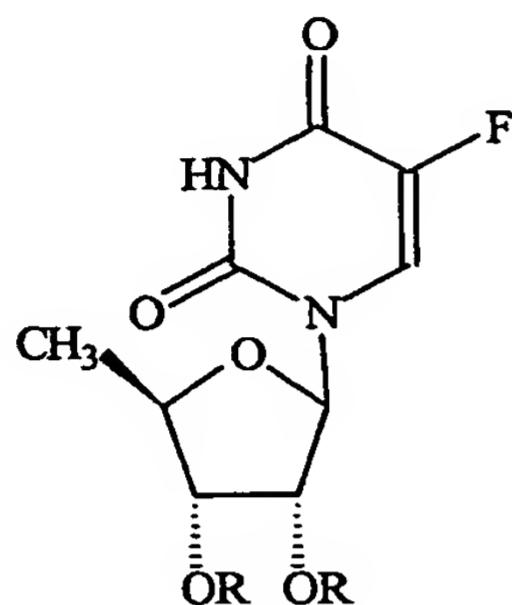
CLAIMS

1. A process for preparing a compound of formula

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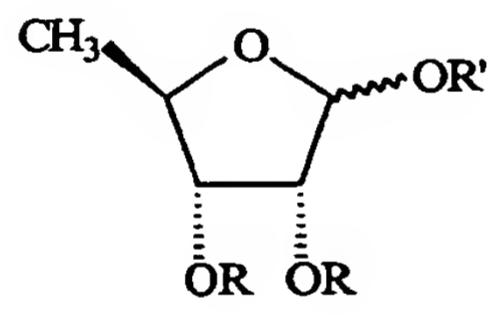
5

(II)

in which R represents linear or branched C<sub>1</sub>-C<sub>5</sub> aliphatic acyl or benzoyl, optionally substituted with C<sub>1</sub>-C<sub>5</sub> alkyls, C<sub>1</sub>-C<sub>5</sub> alkoxy or halogens,

10

which comprises the reaction of coupling of a compound of formula



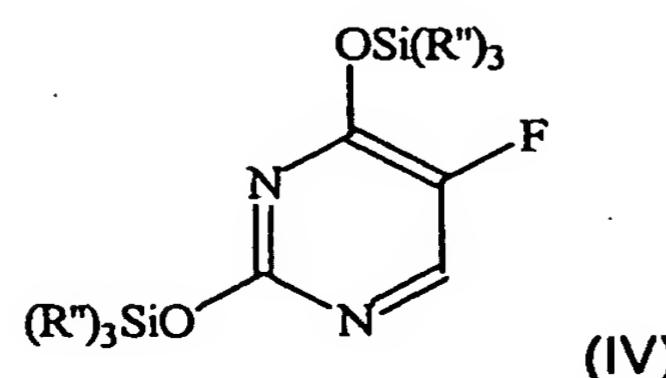
(III)

in which

15 R represents a linear or branched C<sub>1</sub>-C<sub>5</sub> aliphatic acyl or benzoyl, optionally substituted with C<sub>1</sub>-C<sub>5</sub> alkyls, C<sub>1</sub>-C<sub>5</sub> alkoxy or halogens,  
 R' represents R or a linear or branched C<sub>1</sub>-C<sub>5</sub> alkyl,

with a compound of formula

20



(IV)

in which R", being identical or different, represents a C<sub>1</sub>-C<sub>6</sub> alkyl or a phenyl, in the presence of a Lewis acid and in an inert organic solvent, characterized in that said Lewis acid is added at a temperature below -10°C.

5 2. A process according to claim 1 in which said addition of catalyst is carried out at  
a temperature between approx. -15 and -20°C.

10 3. A process according to claim 1 in which, on completion of said addition of catalyst, the reaction mixture is held further at the same temperature.

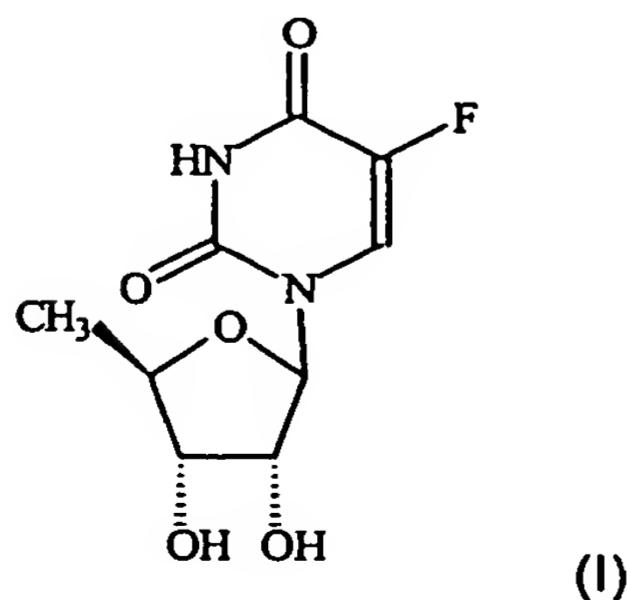
15 4. A process according to claim 1 in which R and R' represent acyl, preferably acetyl, and R" represents methyl.

20 5. A process according to claim 1 in which said Lewis acid is selected from trimethylsilyltrifluoromethanesulphonate and tin tetrachloride, and is preferably tin tetrachloride.

25 6. A process according to claim 1 in which said inert organic solvent is selected from chlorinated solvents or aromatic solvents, preferably chlorinated solvents.

7. A process according to claim 1 in which said compound of formula II, in which R has the meanings stated above, is further submitted to a reaction of deprotection to give doxifluridine of formula I.

8. A process for the preparation of doxifluridine of formula



that comprises a process according to one of the claims from 1 to 7.